UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: 6/25/14

SUBJECT: **Chlorpyrifos:** Reevaluation of the Potential Risks from Volatilization in Consideration of Chlorpyrifos Parent and Oxon Vapor Inhalation Toxicity Studies

PC Code: 059101
MRID No.: 49119501, 49210101
Petition No.: NA
Risk Assessment Type: Single Chemical; Volatilization
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The purpose of this memorandum is to reevaluate the potential human health risks from bystander exposure to the volatilization of chlorpyrifos and chlorpyrifos-oxon emitted from treated fields following the application of chlorpyrifos. The information and conclusions contained in this memo update and supersede those in the January 2013 Preliminary Evaluation

of the Potential Risks from Volatilization[1] assessment. Since the preliminary volatilization assessment was released for public comment in February 2013, new chlorpyrifos and chlorpyrifos-oxon inhalation toxicity data generated using saturated vapor phase administration were submitted to the Agency. The results of these studies have significantly changed how EPA considers the hazard to chlorpyrifos and chlorpyrifos oxon vapor. Based on the new data, there are no human health risks of concern anticipated for volatilization exposure to either chlorpyrifos or chlorpyrifos-oxon.

Volatilization Evaluation

Chlorpyrifos is currently undergoing registration review, EPA's periodic reevaluation of all registered pesticides. As part of registration review, the chlorpyrifos preliminary Human Health Risk Assessment (HHRA) was released for public comment in July 2011.[2] In the preliminary HHRA, potential risks to bystanders from spray drift and exposure from volatilization were identified as possible concerns. The potential risks from spray drift and the impact of potential risk reduction measures were assessed in a July 2012 memorandum[3]. Spray drift is the movement of aerosols and volatile components away from the treated area during the application process. To increase protection for children and other bystanders, chlorpyrifos technical registrants voluntarily agreed to lower application rates and other spray drift mitigation measures[4]. As of December 2012, spray drift mitigation measures and use restrictions appear on all chlorpyrifos agricultural product labels.

In January 2013, a preliminary assessment of the potential risks from volatilization was conducted. The assessment evaluated the potential risks to bystanders, or those who live and/or work in proximity to treated fields, from inhalation exposure to vapor phase chlorpyrifos and chlorpyrifos-oxon emitted from fields following application of chlorpyrifos. The results of the January 2013 assessment indicated that offsite concentrations of chlorpyrifos and chlorpyrifos-oxon may exceed the target concentration based on the toxicological endpoints used at that time. Specifically, for the January 2013 evaluation, points of departure (PoDs) were derived from an acute inhalation toxicity study[5] using aerosolized chlorpyrifos which measured lung, plasma, RBC, and brain cholinesterase (ChE) inhibition; volatilization exposure was assessed only with use of the RBC and lung ChE data.

The January 2013 evaluation identified risks from off-field exposure but one significant area of uncertainty described in the preliminary assessment was the use of the aerosolized chlorpyrifos

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[1] R. Bohaty, C. Peck, A. Lowit, W. Britton, N. Mallampalli, and A. Grube. Chlorpyrifos: Preliminary Evaluation of the Potential Risks from Volatilization. 1/31/2013. U.S. EPA Office of Chemical Safety and Pollution Prevention. D399484, D400781.

[2] Available at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0025.

[3] J. Dawson, W. Britton, R. Bohaty, N. Mallampalli, and A. Grube. Chlorpyrifos: Evaluation of the Potential Risks from Spray Drift and the Impact of Potential Risk Reduction Measures. 7/13/12. U.S. EPA Office of Chemical Safety and Pollution Prevention. D399483, D399485.

[4] R. Keigwin. Spray Drift Mitigation Decision for Chlorpyrifos (059101). 7/2012. U.S. EPA Office of Chemical Safety and Pollution Prevention. EPA-HQ-OPP-2008-0850-0103.

[5] EPA MRID# 48139303**:** Acute Inhalation Exposure of Adult Crl:CD(SD) Rates to Particulate Chlorpyrifos Aerosols: Kinetics of Concentration-Dependent Cholinesterase (CHE) Inhibition in Red Blood Cells, Plasma, Brain and Lung; Authors: J. A. Hotchkiss, S. M. Krieger, K. A. Brzak, and D. L. Rick; Sponsor: Dow AgroSciences LLC.

inhalation toxicity study -- as opposed to chlorpyrifos vapor -- for evaluation of lung ChE resulting from field volatilization. Because field volatilization is the production and release of vapor into the atmosphere after sprays have settled on treated soils and plant canopies, it is well accepted that the vapor, rather than the aerosol, is the relevant form for evaluation of bystander volatilization exposures. However, EPA lacked chlorpyrifos vapor data at the time it conducted the preliminary volatilization assessment in 2013. Following the release of the preliminary volatilization assessment, Dow AgroSciences LLC conducted two, high quality nose-only vapor phase inhalation studies for both chlorpyrifos and chlorpyrifos-oxon[6] to address this uncertainty. In both studies, female rats were administered a saturated vapor, meaning that the test subjects received the highest possible concentration of chlorpyrifos or chlorpyrifos-oxon which can saturate the air in a closed system. At these saturated concentrations, no statistically significant inhibition of ChE activity was measured in RBC, plasma, lung, or brain at any time after the six-hour exposure period in either study. Under actual field conditions, indications are that exposures to vapor phase chlorpyrifos and its oxon would be much lower as discussed in the January 2013 preliminary volatilization assessment. Summaries of the two vapor studies are included as an attachment to this document.

EPA's approach to human health risk assessment follows the four step paradigm established by the NAS (NRC, 1983). These steps include hazard identification, dose-response assessment, exposure assessment, and risk characterization, where risk is a function of both hazard and exposure. In the case of vapor exposure to chlorpyrifos or its oxon from volatilization, the new studies show no effects at saturation concentration in laboratory animals. In other words, no response related to toxicity to chlorpyrifos or its oxon were observed at the highest achievable concentration -- concentrations that likely far exceed those available to bystanders near treated fields. Accordingly, this finding leads to the conclusion that there is no hazard to chlorpyrifos or chlorpyrifos oxon vapor up to the highest possible concentration in the air. As such, if there is no hazard to the vapor for these pesticides, there is no risk. By extension, if there is no risk to chlorpyrifos or chlorpyrifos oxon, there is no need to perform quantitative risk estimates for off-field exposure. Although, in any risk assessment there is some uncertainty associated with extrapolating from laboratory animals to humans, the architecture of the lung is similar between rats and humans[7] and, therefore, the Agency has confidence is this conclusion.

The preliminary volatilization assessment was released for public comment on February 2013 and closed May 2013. During this period comments were received regarding the exposure methodologies employed, and the uncertainties and assumptions in the preliminary volatilization assessment[8]. The Dow studies have made clear that volatilization of chlorpyrifos does not present a risk of ChE inhibition from inhalation of chlorpyrifos vapor, and none of the comments

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[6] W. Irwin. Review of Nose-Only Inhalation of Chlorpyrifos Vapor: Limited Toxicokinetics and Determination of Time-Dependent Effects on Plasma, Red Blood Cell, Brain and Lung Cholinesterase Activity in Femal CD(SD): Crl Rats. U.S. EPA Office of Chemical Safety and Pollution Prevention. 6/25/14. D411959. TXR# 0056694. EPA MRID# 49119501.
W. Irwin. Review of Nose-Only Inhalation of Chlorpyrifos-Oxon Vapor: Limited Toxicokinetics and Determination of Time-Dependent Effects on Plasma, Red Blood Cell, Brain, and Lung Cholinesterase Activity in Female CD(SD):Crl Rats. U.S. EPA Office of Chemical Safety and Pollution Prevention. 6/25/14. D415447. TXR# 0056869. EPA MRID# 49210101.

[7] W. Hofmann, L. Koblinger, T.B. Martonen. Structural Differences Between Human and Rat Lungs: Implications for Monte Carlo Modeling of Aerosol Deposition. Health Physics [1989, 57 Suppl. 1:41-6; Discussion 46-7].

[8] All public comments and related documentation are available in docket EPA-HQ-OPP-2008-0850.

received included data or other information that would suggest that an appropriate vapor study does not represent the best means for assessing the potential for inhalation risk from volatilized chlorpyrifos. While a revised volatilization assessment is no longer needed, the EPA intends to review and respond to comments in a subsequent memorandum.

Attachment – Vapor Inhalation Study Summaries

Citation: Hotchkiss, JA, Nose-Only Inhalation of Chlorpyrifos Vapor: Limited Toxicokinetics and Determination of Time-Dependent Effects on Plasma, Red Blood Cell, Brain and Lung Cholinesterase Activity in Femal CD(SD): Crl RATS (2013), MRID 49119501, Unpublished.

Sponsor: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, Indiana 46268

Summary:

In a special acute inhalation toxicity study (MRID 49119501), chlorpyrifos 97.6% a.i., (CPF, Lot # 7299412; TSN100759) was administered as a saturated vapor to 40 non-fasted Crl:CD Sprague Dawley strain female rats by nose-only inhalation exposure at a time-weighted concentration of 17.7 ppb (0.254 mg/m3) for 6 hours in comparison to control rats with 0 ppb. Rats were sacrificed immediately (0 hr) and at 2, 4, 6, or 12 hours after the end of exposure (n=8/exposure group/sacrifice time). Blood and tissues were isolated and processed to determine cholinesterase (ChE) activity in plasma, red blood cells (RBC), brain, and lung tissue. Whole blood samples from n=4 rats in each experimental group were analyzed to determine the concentration of chlorpyrifos (CPF), oxon and trichloropyrinol (TCP). An additional group of unexposed female control rats (n=8), which experienced the same laboratory and exposure tube acclimation and animal husbandry activities as the control and CPF exposure group animals, were sacrificed at the start of the air and CPF exposures. The oxon content in the chlorpyrifos was <0.1% and 1.4% in the test atmosphere.

No clinical effects indicative of cholinesterase inhibition were noted during the six-hour exposure period. In-life observations noted post-exposure were limited to soiling in four rats exposed to CPF and all rats appeared normal by test day 2. There were no decreases in ChE activity in any tissue which were significantly significant.

In the red blood cell samples, the ChE activity at all time points was comparable to control activity, with none having statistical significance. The ChE activities for the 17.7 ppb samples 0, 2, 4, 6 and 12 hours after exposure were 105.7%, 98.6%, 93.3%, 103.3%, and 110.5% of the 0 ppb control group, respectively.

In the plasma samples, the ChE activity for the 17.7 ppb samples 0, 2, 4, 6 and 12 hours after exposure were 94.9%, 106.3%, 85.8%, 105.4%, and 96.9% of the 0 ppb control group, respectively, with none having statistical significance. A slight decrease in ChE activity was measured at 4 hours post dose, however, it was not statistically significant and the trend was not consistent with the 2-hour and 6-hour results.

In the lung samples, the ChE activity for the 17.7 ppb samples 0, 2, 4, 6 and 12 hours after exposure were 88.6%, 94.8%, 88.8%, 93.8%, and 96.6% of the 0 ppb control group, respectively, with none having statistical significance. The 0 and 4-hour results had activity below 90%, however, this trend was not consistent with the 2, 6 and 12-hour findings.

In the brain samples, statistically significant ChE inhibition was not observed at any time point for the 17.7 ppb samples ChE activity at 0, 2, 4, 6 and 12 hours after exposure was 104.1%, 98.3%, 99.7%, 106.1%, and 101.7% of the 0 ppb control group. The 6-hour sample was the only time point with a statistically significant result, however, it was for an increase in ChE activity, not inhibition.

For chlorpyrifos, the blood levels ranged from the lower limit of quantitation (LLQ) to 0.335 pg/g during the time period after exposure. For TCP, the blood levels ranged from 12.4 to 90.4 pg/g during the time period after exposure. No oxon greater than or equal to the lower limit of quantitation (LLQ; 0.00015 nmole/g blood) was measured in the blood of any control (unexposed or 0 ppb-exposed) or CPF-exposed rat at any time point.

The purpose of the study was to determine pharmacokinetics and ChE inhibition of the RBC, plasma, brain and lung of rats exposed to a single dose of saturated vapor of chlorpyrifos. This purpose was achieved and no meaningful ChE inhibition was observed at the saturation concentration.

This study is classified as acceptable/non-guideline, however, since it was a special study, it does not fulfill any guideline requirement.

Citation: Hotchkiss, JA, Nose-Only Inhalation of Chlorpyrifos-Oxon Vapor: Limited Toxicokinetics and Determination of Time-Dependent Effects on Plasma, Red Blood Cell, Brain, and Lung Cholinesterase Activity in Female CD(SD):Crl Rats. MRID 49210101, Unpublished.

Sponsor: Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, Indiana 46268

Summary:

In a special acute inhalation toxicity study (MRID 49210101), chlorpyrifos oxon (100% purity) was administered as a saturated vapor to 48 female CD(SD):Crl rats for six hours via nose-only exposure. This study was designed to assess the effect of an acute six-hour nose-only inhalation exposure to a saturated vapor concentration of chlorpyrifos oxon (oxon) on cholinesterase (ChE) activity in red blood cells (RBC), plasma, lung, and brain and to determine the blood concentrations of oxon and the metabolite 3,5,6-trichloro-2-pyridinol (TCP) in oxon-exposed rats. Female CD(SD):Crl rats were exposed six consecutive hours to filtered air (control) or a time-weighted average concentration of 35.3 $\mu g/m^3$ (2.58 ppb) oxon vapors using a flow-past nose-only inhalation exposure system. Rats were sacrificed immediately (0 hr) and 1, 2, 4, 8, or 24 hours after the end of exposure (n=8/exposure group/sacrifice time). Blood and tissues were isolated and processed to determine ChE activity in RBC, plasma, lung, and brain tissue. Oxon and TCP concentrations were determined in whole blood samples from four rats in each experimental group/sacrifice time.

During or after oxon exposure, no clinical signs of toxicity were noted in oxon-exposed rats at any time. There were no statistically significant decreases in ChE activity in any tissue

monitored. The only statistically significant changes in cholinesterase (ChE) activity were in the RBC and brain, however, increases of ChE activity occurred.

In the red blood cell samples, the ChE values for the 35.3 $\mu g/m^3$ samples at 0, 1, 2, 4, 8 and 24 hours after exposure were 93.6%, 110.6%, 113.9%, 116.5%, 102.2%, and 111.9%, respectively, of the 0 $\mu g/m^3$ control group, with none having both statistical significance and an activity decrease greater than 10%. The RBC ChE activity at 4 hours was statistically significant, however it was an increase in activity.

In the plasma samples, the ChE values for the 35.3 $\mu g/m^3$ samples at 0, 1, 2, 4, 8 and 24 hours after exposure were 103.0%, 107.5%, 101.5%, 136.7%, 101.0%, and 127.6%, respectively, of the 0 $\mu g/m^3$ control group, with none having statistical significance nor a decrease in ChE activity.

In the lung samples, the ChE values for the 35.3 $\mu g/m^3$ samples at 0, 1, 2, 4, 8 and 24 hours after exposure were 93.7%, 108.3%, 118.6%, 109.1%, 101.7% and 91.6%, respectively, of the 0 $\mu g/m^3$ control group, with none having statistical significance nor a decrease in activity greater than 10%.

In the brain samples, the ChE values for the 35.3 $\mu g/m^3$ samples at 0, 1, 2, 4, 8 and 24 hours after exposure were 100.5%, 106.2%, 102.0%, 100.9%, 101.2%, and 101.0%, respectively, of the 0 $\mu g/m^3$ control group, with none having both statistical significance and an activity decrease. The brain ChE activity at 1 hour was statistically significant, however it was an increase in activity.

At any time after exposure, no oxon was measured in the blood (lower-limit of quantitation; LLQ = 0.118 ng/g blood), however, blood TCP levels > LLQ (2.44 ng/g blood) were measured at the end of exposure and through eight hours post-exposure. No statistically significant inhibition of ChE activity by oxon was measured in RBC, plasma, lung, or brain at any time after exposure. The presence of TCP in the blood of oxon-exposed rats confirms that inhaled oxon vapor is absorbed by the respiratory tract, however, the oxon is rapidly metabolized to TCP and the oxon is not systemically bioavailable at blood levels ≥ the LLQ of 0.118 ng/g blood (3.53x10-4 nmole/g blood). The six-hour No Observed Effect Concentration (NOEC) for inhaled oxon vapor is > 35 μg oxon/m^3 air, based on the absence of statistically-significant cholinesterase inhibition in RBC, plasma, brain, or lung (the portal-of-entry tissue). The results of this study suggest that there is no cholinesterase-based hazard from inhalation of a saturated vapor concentration (35.3 $\mu g/m^3$) of chlorpyrifos oxon.

The purpose of the study was to determine pharmacokinetics and ChE inhibition of the RBC, plasma, brain and lung of rats exposed to a single dose of saturated vapor of chlorpyrifos. This purpose was achieved and no meaningful ChE inhibition was observed at the saturation concentration.

This study is classified as acceptable/non-guideline, however, since it was a special study, it does not fulfill any guideline requirement.